REMARKS

Reconsideration is requested.

Claims 1-67, 71-72, 75, 78, 80-84 and 90-94 have been canceled, without prejudice. Claims 68-70, 73, 74, 76, 77, 79, 85-91 and 95-101 are pending.

The Examiner is requested to confirm receipt of the certified copy of the priority document. The certified copy of the priority document was filed in the parent application Serial No. 08/612,973, as acknowledged by Examiner Zeman in the attached first page of the Office Action dated May 19, 1999, in the parent application Serial No. 08/928,017.

Claims 73 and 76 have been amended above to obviate the objections of the same found in paragraphs 2-4 on page 2 of the Office Action dated January 14, 2004 (Paper No. 24). Withdrawal of the objections to claims 73 and 76 is requested.

The Section 102 rejection of claims 70, 73, 75, 76, 87 and 95-97 over Watanabe (U.S. Patent No. 5,610,009), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner's comments appear to be similar to the comments made in paragraphs 43-45 of the Office Action dated April 21, 2004 (Paper No. 18).

The Applicants believe that Watanabe discloses an internal deletion from the HCV E1 protein covering amino acids 260-296 of the HCV polyprotein. The Examiner has previously stated in paragraph 44 of Paper No. 18 that the presently claimed invention is "interpreted as a living recombinant vector carrying a fragment of HCV E1 protein, wherein the E1 protein fragments range from 192-400, more particularly in the region between positions 250-341. Furthermore, the E1 protein contains a deletion in which the hydrophobic domain of amino acid residues between positions 264-293, plus

or minus 8 amino acids (272-301 for plus amino acids or 256-285 for minus 8 amino acids by calculation or 256-301 by adding 8 amino acids at the 5' and minus 8 amino acids at the 3' or 242-350 vice versa), preferably, the E1 is SEQ ID NO:1 or part thereof."

The Applicants therefore believe that the Examiner has interpreted "264-293 plus or minus 8 amino acids" as including the following possibilities:

1. 264-293
2. 272-301
3. 256-301
4. 242-350.

The Applicants request clarification as to the Examiner's inclusion of "242" and "350". Moreover, the Applicants believe the recited "plus or minus 8 amino acids" should be broadly interpreted as at least including the following possibilities:

1. 264-293
2. 264-285
3. 264-301
4. 272-293
5. 272-285
6. 272-301
7. 256-293
8. 256-285
9. 256-301

Even if construed in its broader sense, none of the claimed possibilities are believed to be identical to the deletion of the cited prior art covering amino acids 260-296 such that the cited art is not believed to teach each and every aspect of the presently claimed invention. The claimed invention therefore is submitted to patentable over Watanabe.

The Examiner's further reference to clone pHCV 416 in paragraph 6 of Paper No. 24 is not understood and clarification is requested as follows.

Initially, the Applicants believe the Examiner's reference is to clone pHCV 419 given the Examiner descriptions of amino acid residues 192 to 256, 294 to 336 and 393 to 654. See, Column 12, lines 51-52 of Watanabe relating to pHCV 419, as compared with Column 12, lines 27-28 relating to pHCV 416. More importantly, the Examiner's reliance on reference to either pHCV 419 and/or pHCV 416 is unclear as the same appears to be a further indication of an internal deletion covering amino acids 260 to 296, which, as described above, is not a teaching of the presently claimed invention. The claims are submitted to be patentable over Watanabe.

Claims 68-70, 73-74, 76, 79, 87, 88, 91 and 95-96 are submitted to be patentable over the combination of Lanford (Virology 1993, Volume 197, pages 225-235), Ralston (Journal of Virology 1993, Volume 67, pages 6753-6761), Watanabe and Ford (Protein Expression and Purification 1991, Volume 2, pages 95-107). Reconsideration and withdrawal of Section 103 rejection of the noted claims over the cited combination of the art are requested in view of the following distinguishing comments.

The Examiner asserts that Lanford allegedly teaches all the limitations of claims 68, 69, 70, 73, 87, 95, 96 and 97. The Examiner does not separately however assert

that these claims are anticipated by Lanford. See, paragraph 11 of Paper No. 24. The Examiner further asserts that Ralston "meet[s] the limitation of [claims] 68 and 88." See, paragraph 12 of Paper No. 24. The Examiner does not separately make a rejection of these claims under Section 102 over Ralston. Similarly, the Examiner asserts that the "limitation of claim 74" is taught by Ford. See, paragraph 13 of Paper No. 24. Finally, the Examiner asserts that the "limitation of claim 70" is allegedly taught by Watanabe. See, paragraph 14 of Paper No. 24.

The Examiner then concludes that "it would have been obvious to one of ordinary skill in the art at the time of the invention was filled [sic, filed] to be [sic, have been] motivated by the recited references and to combine [sic, have combined] the disclosure taught by Lanford et al., Ralston et al., Watanabe et al. and Ford et al. to make [sic, have made] a recombinant vector for expressing an HCV E1 protein fuse with a histadine tails and its C-terminal and further containing a truncation in the hydrophobic domain as taught by Watanabe et al. with highly expected result." See, paragraph 15 of Paper No. 24.

The Examiner's combination of 4 references to allege the obviousness of the presently claimed invention fail to provide a prima facie case of obviousness and the Section 103 rejection should be withdrawn. The Examiner's apparent picking and choosing of details from references is believed to be inappropriate and the cited art is not believed to have provided a motivation to one of ordinary skill in the art to have made the presently claimed invention.

Initially, the Applicants note the Examiner describes Lanford as teaching a vector as a baculovirus vector for expression in insect cells. Claim 68 recites a vaccinia virus

vector. Moreover, Lanford does not teach an internal deletion of claim 70 or the invention of claim 69. Further, Lanford is understood to describe at least one major drawback for using insect cells for expression of the HCV E1 envelope protein. Specifically, Lanford is understood to describe inappropriate processing as one drawback. See, page 233, right column, second sentence of the second full paragraph of the reference. While admitting the problem with expression in insect cells, Lanford does not provide or suggest a possible alternative. See, page 223, right column, last sentence of the second full paragraph of the cited art. The Examiner apparently relies on Ralston and Watanabe to provide the missing elements of Lanford. The secondary references however fail to cure the deficiencies of Lanford, as further detailed below.

The Examiner appears to rely on Ralston for a teaching a vaccinia viral vector to allegedly teach specific aspects of claims 68 and 88. The Applicants believe Ralston discloses vaccinia viral vectors for expression of the HCV E1 envelope protein comprising either one of the nucleic acid sequences covering amino acids 1 to 906 (entire core + entire E1 + entire E2 + entire p7 + part of NS2), amino acids 1 to 304 or amino acids 1 to 381 (entire core + part of E1), and amino acids 347 to 906 (part of E1 + entire E2 + entire p7 + part of NS2). Claim 68 relates to a vaccinia viral vector for expression of the HCV E1 envelope protein comprising a nucleic acid sequence covering a region starting between 117 to 192 and ending between 250 to 400. Claim 69 relates to a recombinant vector for expression of the HCV E1 envelope protein in lower eukryotic or mammalian cells comprising a nucleic acid sequence covering a region starting between 117 to 192 and ending between 263 to 400. As the boundaries disclosed by Ralston are different from the presently claimed regions, it is unclear to the

Applicants how Ralston could teach or suggest the aspects of the present claims. Moreover, claim 70 relates to a recombinant vector for expression of an HCV E1 envelope protein with an internal deletion. As Ralston fails to teach or suggest internal deletions it is unclear how Ralston teaches or suggests the presently claimed invention, alone or in combination with any of the other three cited references.

The Examiner is urged to appreciate that an advantage of the presently claimed recombinant vectors, which was unexpected, resides in omission of a large part of the Core region from the recombinant nucleic acid encoding the HCV E1 envelope protein. See, de Martynoff et al (1997, Viral Hepatitis and Liver Disease, Proceedings of IX International Symposium on Viral Hepatitis and Liver Disease. Rome, Italy, 21-25 April 1996. Edizioni Minerva Medica Turin 1997, pages 219-224) (a copy of which will be submitted under separate cover). This publication largely teaches the presently disclosed invention and the nomenclature of the constructs in this article is the same as in the present disclosure. More specifically, the reference discloses that "the single E1 and E2 envelope proteins [with a 22-amino acid or 73-amino acid C-terminal domain of Core upstream of E1] were produced at high level as compared with the polyprotein constructs starting at the natural HCV initiation codon [i.e., starting at position 1]." All E1-expression constructs of Ralston on the other hand start at the natural HCV initiation codon. The above-described advantage of the presently claimed invention is not disclosed by or suggested by Ralston or any of the other cited art. This advantage, for example, is not apparent from, or suggested by, Lanford, Watanabe or Ford.

The claimed invention is submitted to be patentable over the Examiner's cited combination of art.

The deficiencies of Watanabe are described above. Moreover, the construct apparently referred to by the Examiner in Watanabe, that is pHCV419 (amino acids 192-259/297-336/393-654) inevitably is believed to lead to the expression of an uncleavable E1-E2 fusion protein (see, column 14, lines 56-61 of Watanabe). In addition, Watanabe conclude that a very large part of E2 is required downstream of E1 to obtain efficient expression of E1, more specifically constructs pHCV420 (amino acids 192-654) or pHCV421 (amino acids 192-654 with internal deletion of amino acids 260-296) as compared to construct pHCV172 (amino acids 192-336) (see, column 15, lines 2-6). All of these elements are believed to teach away from the presently claimed invention as in the current invention an HCV E1 envelope protein is obtained from which flanking core- or E2-sequences, if present, are cleaved during expression, and if at all present, only a limited part of the E2 protein is encoded by the recombinant construct (up to amino acid 400, E2 starts at amino acid 384).

Furthermore, it is believed to be known from Ralston that co-expressed E1 and E2 form co-purifying complexes (see, fourth and sixth sentence of Abstract of Ralston (1993)). This is an unwanted effect hindering the purification of E1.

In view of all the above, the Applicants respectfully submit that the claims are patentable over the Examiner's combination of art and withdrawal of the Section 103 rejection of the noted claims is requested.

Reconsideration and withdrawal of the Section 112, first paragraph, rejection of claims 77 and 98-100 is requested. The Examiner's apparent requirement for FDA approval in paragraph 20 on page 6 of Paper No. 24 is not believed to be the standard

for enablement or written description. Reconsideration and withdrawal of the Section 112, first paragraph, rejection are requested.

The Section 112, second paragraph, rejection of claims 95-98 and 100 is traversed. Reconsideration and withdrawal of the rejection are requested as the Applicants believe, for example, the paragraph bridging pages 3-4 of the specification make clear that parts of the nucleotide sequences recited in claims 95-97 will be understood to encode at least one HCV epitope of the E1 region. The claims are submitted to be definite, especially in light of the specification. Withdrawal of the Section 112, second paragraph, rejection of claims 95-98 and 100 are requested.

The application is submitted being in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned if anything further is required in this regard.

Respectfully submitted,

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